clinical grounds for advancing this theory. I have also suggested the possibility of the ganglia of the glossopharyngeal and vagus nerves playing a role in the symptomatology of the syndrome, and emphasized the great importance, clinically, of vagus symptoms in this relation.

A particular emphasis has also been given to the occurrence of mild inflammatory reactions in ganglia above or below the chief focus, or that giving rise to the eruption of herpes zoster (*eruptive focus*). The symptoms present in the non-eruptive zones are mild and transitory in nature, and consist of pains and slight objective sensory disturbances. I regard the Gasserian, geniculate, acoustic, glossopharyngeal, vagus, second, third, and fourth cervical ganglia as representing a continuous ganglionic series or chain, all having the same embryonal origin (*neural ridge*), and all, with the exception of the acoustic ganglia, having the same cell type (unipolar), and therefore belonging to the realm of posterior poliomyelitis. This serial chain of ganglia is concerned in the production of the syndrome. A hemorrhagic inflammation in one of these ganglia is followed by the usual manifestation of herpes zoster, an eruption appearing in its respective zone.

Depending upon the severity of the infection, other ganglia of the group may be the seat of an inflammatory reaction as well, but not sufficient in degree to produce an eruption. This milder involvement is manifested clinically by pains and slight objective sensory disturbances, and in the case of the geniculate and acoustic ganglia, by their respective neural symptoms.

THE PRESENT STATUS OF EXPERIMENTAL ARTERIAL DISEASE.[1]

By I. Adler, M.D.,
of New York.

For a long time the problems, both clinical and pathological, involved in the question of arteriosclerosis have received considerable attention on the part of the investigator, the clinician, and the practitioner. The saying that "a man is as old as his arteries" has become public property, not only of the medical, but also of the lay world, and passes almost as an axiom today.

An enormous literature has sprung up on arteriosclerosis, and it has been attacked by many brilliant and indefatigable workers from the clinical and histological as well as from the experimental side, without, however, it must be confessed, any unanimity of view or clearness of conception being attained. It was, therefore, hailed by many as the beginning of a new era in the study of arteriosclerosis when Josué,[2] in 1903, reported that he had artificially produced arteriosclerosis, or, as he called it, "atheroma," in the aorta of rabbits by intravenous injections of adrenalin. The matter was at once taken up by investigators in many countries. Erb,[3] Külbs,[4] Kurt Ziegler,[5] v. Rzentkowski,[6] Fischer,[7] Scheidemantel,[8] D'Amato,[9] Pearce and Stanton,[10] Lissauer[11], Baylac and Albarede,[12] Biland,[13] and others have in the main verified and somewhat added to Josué's results

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[1] Read at a meeting of the New York Academy of Medicine, March 19, 1908.

The lesions thus produced are very characteristic, and on superficial view seem to resemble closely atheromatous degeneration in the human aorta. Their site of predilection is the ascending portion and the arch of the aorta; in more advanced cases the descending portion is involved. The abdominal aorta is the last to suffer, and extensive lesions there are rather exceptional. A few cases, however, have been reported in which the entire aorta from its origin down into the iliacs has been converted into a rigid tube of degeneration.

The lesions appear as larger or smaller patches of peculiar translucent appearance and rough surface; in the advanced stages the edges are somewhat raised above the level of the inner surface of the vessel, while the centre is usually depressed; the vascular walls are distinctly thinner than normal in and about these patches, and thus tend to the formation of aneurysmatic dilatations and pouches. It should be noted that the aneurysmatic dilatation never involves the entire circumference of the vessel, but is a partial bulging corresponding to the location of more or less intensely degenerated patches. Erb, Fischer, and Ziegler have noted cases of dissecting aneurysm. As a rule, calcification appears at a very early stage of the process.

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[2] Atherome aortique expérimentale, Presse médicale, 1903, 1904, p. 798.

[3] Experimentelle und histologische Studien über Arterienerkrankung nach Adrenalininjektionen. Arch. f. exp. Path. u. Pharm. 1905, liii, 173.

[4] Experimentelle Studien über die Wirkung der Nebennierenextrakte. Arch. f. exp. Path. u. Pharm., 1905, liii, 140.

[5] Ueber die Wirkung intravenöser Adrenalininjektionen auf das Gefäss-system und ihre Beziehung zur Arteriosklerose. Ziegler's Beiträge, 1905, xxxviii, 229.

[6] Atheromatosis aortæ bei Kaninchen nach intravenösen Adrenalininjektionen. Berl. klin. Woch., 1904, 830.

[7] Ueber Arterienerkrankungen nach Adrenalininjektionen. Kongress f. innere Medizin, 1905, 236.

[8] Ueber die durch Adrenalininjektionen zu erzeugende Aortenverkalkung der Kaninchen. Virchow's Arch., 1905, clxxxi, 363.

[9] Weitere Untersuchungen über die von den Nebennieren Extrakten bewirkten Veränderungen der Blutgefässe und anderer Organe. Berl. klin. Woch., 1906, Nrs. 33, 34.

[10] Experimental Arteriosclerosis. Jour. Exper. Med., 1906, viii, 74.

[11] Experimentelle Arterienerkrankungen beim Kaninchen. Berl. klin. Woch., 1905, p. 675.

[12] Recherches expérimentales sur l'atherome de l'aorte consécutif a l'action de l'adrenaline. Compt. rend. de la soc. de biol., 1904, lvii, 640.

[13] Ueber die durch Nebennieren praparate gesetzten Gefäss und Organveränderungen. Deut. Arch. f. klin. Med., 1906, lxxxvii, 1906, p. 413.

The yellow patches of fatty degeneration and the so-called gelatinous patches, so frequent and constant in human atheroma, have, so far as I know, never been found in these experimental affections of the rabbit's aorta, nor do the patches just described ever seem to lead to ulceration.

Almost all investigators have found these lesions confined to the aorta, no matter how long the animals have been subjected to treatment. Erb, it is true, reports some lesions in other vessels, iliacs and carotids, but no other observer has been fortunate enough to meet with similar results. Once or twice slight degeneration of the pulmonary artery has been noted. The fact that many rabbits subjected to intravenous injections of adrenalin die very suddenly of cerebral hemorrhage suggests the strong probability of damage to the smaller cerebral vessels, but as yet no one has been able to detect any palpable lesions.

All observers are pretty well agreed on the histology of these lesions. The degeneration is primarily and mainly located in the media. The first change that occurs is necrosis of the smooth muscle cells, and as they are destroyed, the elastic fibers, deprived of the support of the muscle cells and no longer able alone to withstand the pressure, are first stretched to their utmost limit and then snapped and broken. There is still some doubt whether the elastic fibers themselves degenerate, although it is probable that, together with the tension and the metabolic changes going on within the vessel wall, some fatty degeneration of the elastic fibers does take place. Calcareous deposits very soon appear within the areas of necrotic and destroyed cells and fibers. No inflammatory process can be observed during all these changes. Leukocytic emigration in the outskirts of the patch, with an occasional giant cell, is occasionally seen, but only after calcification is complete or nearly so. The whole is distinctly a necrotic and not an inflammatory process, and is in the main strictly confined to the media. The intima seems not to be largely involved. In those places where considerable depression occurs together with distention of the vessel wall, some hypertrophy of the intima takes place, but degeneration or ulceration of the intima has not been observed.

It was very soon found that the suprarenal extracts—adrenalin, suprarenin, perinephrin, and others—were not the only substances that produce the peculiar effects in the aorta of rabbits. A number of other substances that tend to raise blood pressure produced the same results. Fischer obtained positive results with digalen, Miller[14] with barium chloride, Bennecke[15] with barium chloride, hydrastin, and hydrastinin, Sturli[16] with methylamino-acetobrenzkatechin, which is also a vasoconstrictor and pressure raiser. Some years ago I[17] fed tobacco infusion to rabbits, with a view of testing the effect on the bloodvessels. Interesting changes in the liver and in the smallest vessels were found, but none in the aorta. After the appearance of Josué's paper, in association with Dr. Hensel,[18] I injected pure nicotine, also a decided blood pressure raiser, into the ear vein of rabbits, with positive results. Miller also obtained positive results with nicotine. Boveri[19] obtained positive results with infusion of tobacco by the mouth. Gouget[20] treated rabbits with infusion of tobacco by the mouth and intravenously and with a combination of both. Baylac[21] obtained positive results by intravenous as well as by subcutaneous administration of tobacco infusion. Quite recently Rickett[22] evidently unaware of our experiments, obtained positive results with nicotine and with infusion of tobacco intravenously.

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[14] Experimental Arterial Degeneration. Amer. Jour. Med. Sci., 1907, p. 593.

[15] Studien über Gefässerkrankungen durch Gifte. Virchow's Arch., 1908, cxci, 202.

[16] Gefässveränderungen nach Injektionen von Methylamino-acetobrenzkatechin. Münch. med. Woch., 1905, 630.

All the substances mentioned thus far have one quality in common —they are more or less decided raisers of blood pressure; and the conclusion naturally suggests itself that the effect obtained is produced by the blood-pressure-raising quality of the drugs employed. This fits in very nicely, too, with the prevailing theories of human arteriosclerosis, and many authors build far-reaching theories and hypotheses on this basis. A closer scrutiny of the facts shows this view, however, to be untenable.

Mironescu[23] experimenting with euphthalmin, which is said to depress blood pressure as violently and suddenly as adrenalin raises it, comes to the conclusion that it is not the rise in blood pressure, but the sudden variations in pressure that produce the effect. D'Amato experimented with paraganglin, which, as he proved by manometric tests, does not raise the blood pressure. The paraganglin was given intravenously as well as by the mouth, and he obtained results similar to those with adrenalin. When given by the mouth it was necessary to employ much larger doses. D'Amato is inclined to look upon the action as purely toxic, and claims a special affinity of paraganglin for the smooth muscle, he having found slight degrees of necrosis in the muscles of the stomach and intestine, as also in the bladder, when given by the mouth. Braun[24] gave amyl nitrite and adrenalin together intravenously and obtained positive results, though he had shown by careful manometric measurements that this combination does not alter the blood pressure; he is, therefore, convinced that the positive results obtained were caused by toxic action. Fischer obtained positive results with a great variety of substances, a large number of which, such as acids, ferments, and even normal saline, had little or no effect upon blood pressure. Kolisch[25] claims positive results with phloridzin and phloretin, both of which are said to have no effect on blood pressure. Boveri injected carbonate of lead in physiological salt solution in three rabbits, and found dilatations, thickenings, calcifications, and aneurysms. He also experimented on 6 rabbits with putrid material, partly through a stomach tube and partly subcutaneously, obtaining positive results in three, while the other three showed no lesions. Fischer writes that he has produced aneurysms without calcification and with but very little change apparent to the naked eye in rabbits by the injection of various metallic salts. (I have been unable to find any detailed account of these experiments.) It might be mentioned in this connection that Koranyi[26] claimed that iodine, especially in the form of iodipine, inhibited the action of adrenalin on the rabbit's aorta. As this seemed to supply an experimental basis for the popular treatment of arteriosclerosis, it created quite a sensation. It was tested by many, especially by Loeb and Fleisher[27] who, after very careful experiments on a large number of rabbits, could find no palpable influence of the iodides upon the action of adrenalin. This seems now to be the general opinion. In a later publication Koranyi[28] claims that it is not the iodine, but the oil, which tends to neutralize the effect of the adrenalin.

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[17] Some Effects of Tobacco on the Tissues of Rabbits. Jour. Med. Research, viii, No. 2.

[18] Intravenous Injections of Nicotine and Their Effects upon the Aorta of Rabbits. Jour. Med. Research, September, 1906, v, No. 2.

[19] Contributo allo Studio degli Atheromi aortici sperimentali. Clinica med. Ital., 1906, xlv, 41.

[20] Sur quelques lésions de l'intoxication tabagique expérimentale. Presse méd., 1906, No. 67, 533.

[21] Athérome expérimental de l'aorte consécutif a l'action du tabac. Compt. rend. de la Soc. de biol., 1906, lx, 935.

[22] Experimental Atheroma. Jour. Path. and Bact., October, 1907, xii, No. 1.

[23] Beiträge zur Wirkung des Adrenalins und Euphthalmins auf den Blutdruck beim Kaninchen. Zntralbl. f. innere Med., 1906, 598.

[24] Zur Frage der Arteriosklerose nach intravenöser Adrenalinzufuhr. Münch. med. Woch., 1905, p. 533.

Morelli[29] a pupil of Koranyi, working with digalen, finds that sesame oil prevents its action upon the rabbit's aorta. According to Bennecke, spermin counteracts to some extent the action of hydrastinine. On the other hand, Hedinger and Loeb[30] encountered the typical aortic lesions in rabbits treated with subcutaneous injections of KI, but all their further experiments with the iodides proved negative. We should mention also the work of Loeb and Githens[31] concerning the effect of intravenous injections of adrenalin in rabbits with experimental nephritis, in others after thyroidectomy, and in pregnant animals, with a view of testing the effect of these injections both on the mother and on the developing bloodvessels of the fœtus. They also studied the effect of pyrokatechin.

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[25] Ueber durch Phloridzin hervorgerufene Aortenveränderungen. Münch. med. Woch., 1905, p. 2446.

[26] Ueber die Wirkung des Iods auf die durch Adrenalin erzeugte Arterionekrose. Deutsch. med. Woch., 1906, Nr. 17.

[27] Ueber den Einfluss von Iodpräparaten auf die durch Adrenalininjektionen hervorgerufenen Gefässveranderungen. Deutsch. med. Woch, 1907, Nr. 10, 382,.

[28] Berichtigung zu meiner Mitteilung über die Wirkung des Iods auf die durch Adrenalinerzeugte Arterionekrose. Deutsch. med. Woch., 1907, Nr. 5.

[29] Ueber Arterionekrose. Berl. klin. Woch., 1908, Nr. 8, 398.

[30] Ueber aortenveränderungen bei Kaninchen nach subkutaner Iodkaliverabreichung. Arch. f. exp. Path., 1907, lvi, 314.

[31] The Effect of Experimental Conditions on the Vascular Lesions Produced by Adrenalin. AMER. JOUR. MED. SCI., October, 1905, 403.

We have thus a rather large group of substances, some tending to raise blood pressure, some having no effect at all upon it, some few even lowering it, but all producing very similar, it may be said practically identical, effects upon the aorta of rabbits. They all primarily affect only the media, causing necrosis with degeneration and calcification of the smooth muscle fibers, stretching and breaking up of the elastic fibers, and, when the intima is at all affected, it is simply in the form of more or less secondary and compensatory thickening, never associated with any degeneration or ulceration, the entire process resembling that described by Mönckeberg[32] in human peripheral vessels.

In order to arrive at a just valuation of these experimental results a number of other facts must be noted. In the first place, it must be stated that the lesions described have been obtained only in rabbits. All efforts to produce similar affections in other animals, as dogs (Pearce and Stanton, Fischer, v. Rzentkowski, and others) and monkeys (Erb), have utterly failed. Even in rabbits, however, there is apparently no constancy or regularity in the effect, and it is impossible to predict the result of any experiment, no matter what substance is used.

Kaiserling[33] experimented on 8 rabbits with adrenalin, one of which received as many as 66 injections, with absolutely no macroscopically visible lesions, and under the microscope nothing was to be seen except a slight stretching of the elastic fibers.

It is to be regretted that many observers give no details of their experiments, but all that do, report a varying number of negative as well as positive results. Again, it is generally recognized that the positive results obtained are very frequently in no proportion to the number of injections or to the duration of the experiment. Erb has seen extensive calcification of the entire aorta down to the iliacs after one single injection of adrenalin. It is a common experience to have extensive calcareous patches after but comparatively few injections, and no lesions after numerous injections and prolonged treatment. Adler and Hensel found calcification and aneurysms after only 18 injections of nicotine, and no gross lesions whatsoever after as many as 117 nicotine injections.

Josué called attention to the fact that the age and weight of the rabbit are important factors; that the results are more likely to be positive in old animals than in young ones. This seems, on the whole, to be borne out by the results of subsequent research. Pic and Bonnamour[34] injected two young rabbits, weighing under 2000 grams for three months with adrenalin, with no visible effect. Older and heavier animals weighing over 2000 grams gave positive results after a comparatively short time. They found too, that rabbits artificially made tuberculous, or whose power of resistance was impaired, for example, by lactation, responded more readily to adrenalin. Their experiments, however, are too few in number to be convincing. Fischer, however, arrives at similar conclusions.

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[32] Ueber die reine Mediaverkalkung der Extremitätenarterien und ihr Verhalten zur Arteriosklerose. Virchow's Arch., 1903, clxxi, 141.

[33] Beiträge zur Wirkung intravenoser Suprarenininjektionen auf die Kaninchenaorta. Berl. klin. Woch., 1907, Nr. 2, 29.

On the other hand, there are reports of old animals showing nothing, and of young animals with positive results. Thus, Kurt Ziegler found calcareous patches in the abdominal and thoracic aorta with aneurysmatic dilatation in a rabbit only eight weeks old that had been injected only for ten days, while an old animal that had been injected with adrenalin intravenously for six and a half months and subcutaneously for another three and a half months, the entire experiment lasting ten months, showed no gross lesions and but very slight microscopic changes.

In view of these irregular and contradictory results, the question suggested itself to many investigators: Are we really producing an experimental effect by our intravenous and subcutaneous injections? Is it not possible, nay, even probable, that our so-called positive results are the natural outcome of spontaneous disease of the rabbit, and have no relation whatever to our experimental treatment?

It is beyond doubt that arterial disease does occur spontaneously in animals. Lyding,[35] for instance, finds in the ox and in the horse aortic disease very much like human arteriosclerosis, and in the dog a condition in many respects similar to the lesions in the rabbit's aorta. The necessity for investigating this question in the rabbit is obvious. Hedinger and Loeb examined about 100 rabbits that had not been used for experimental purposes, but could find no gross aortic lesions. Von Rzentkowski examined 10 rabbits, with the same negative result; Adler and Hensel, 14 rabbits, all fully grown, some of them old and all weighing over 2000 grams, without being able to detect any macroscopic lesions in the aorta. Fischer states positively that he has found in a number of rabbits (he gives no figures), especially in such as have died from some form of cachectic disease, spontaneous aortic lesions exactly identical, macroscopically and microscopically with those found after adrenalin injections. Bennecke examined 400 rabbits not used for experiment, and found typical aortic lesions of various degrees of intensity in 12 (3 per cent). Quite recently Amy B. Miles[36] published some very startling figures: 61 rabbits were treated with intravenous injections of adrenalin; of these, only 17 (27.86 per cent.) showed macroscopically visible lesions. Of 49 normal rabbits obtained from the same source, kept under the same conditions, and not experimented upon, 17 (34.77 per cent) showed macroscopic lesions. (Nothing is mentioned concerning age and weight of the animals.) The lesions in both sets were identical and of the usual type. When one considers the many thousands of rabbits that have been used for experiment and dissection, it is certainly astonishing, in the light of the statistics of Dr. Miles, that spontaneous aortic disease has not more often been encountered before this. Possibly these lesions may frequently have been overlooked, no special attention being paid to the condition of the vascular system. It is highly probable that breed, environment, food, age, and general condition are important and insufficiently studied factors concerned in the development of spontaneous aortic lesions in the rabbit. That, however, aortic lesions do occur spontaneously in rabbits, and more often than one would have imagined, seems certain.

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[34] Contribution a l'étude du determinisme de l'atherome aortique experimental. Soc. de Biol., 1005, 219.

[35] Zur Kentniss der Arteriosklerose bei Hausthieren. Zeits. f. Thiermed., Band ii, p. 359.

[36] Spontaneous Arterial Degeneration in Rabbits. Jour. Amer. Med. Assoc., October 5, 1907, p. 1173.

The experiments dealing with bacteria and their toxins had best be grouped into a separate class. They are as yet but few in number, but promise, if continued, most valuable results. The changes found in the rabbit's aorta in most of these experiments are said to be different from the adrenalin type, and to resemble more nearly human arteriosclerosis. Thus Gilbert and Lion[37] as early as 1889, injected typhoid bacilli into the ear vein of a rabbit whose aorta had previously been injured. They found at the place of injury a plaque surrounded by a zone of inflammatory material involving both the intima and the media, with a central depression and calcification, particularly in the media. In another rabbit whose aorta had not been injured, injected with a malignant bacillus isolated from man, they found also a plaque in the aorta, but no calcification; there was a distinct hyperplasia of the intima almost purely of connective tissue. They state distinctly that in location, in gross appearance, and in histological structure it approached very closely the arteriosclerosis of the human aorta, and they consider their experiments a proof that infectious disease may be the cause of arteriosclerosis. O. Klotz,[38] besides experimenting with adrenalin under various conditions, and in the main verifying the results of others, obtained important results with the typhoid bacillus and the streptococcus. These, injected into the ear vein of rabbits, seemed to produce changes in the aorta and *in the pulmonary artery* closely resembling the conditions found in arteriosclerosis of the human aorta. There were no aneurysms and no calcification, but fatty degeneration of the endothelial cells and a hyperplasia of connective tissue taking the place of the degenerated material. He also described splitting of the external elastic lamina similar to that described by Jores in human vessels. The injection of diphtheria toxin seemed to affect only the first portion of the aorta and produce lesions similar to those produced by adrenalin.

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[37] Arterites infectieuses expérimentales. Compt. rend. Soc. de Biol., 1889, p. 583.

[38] A Discussion on the Classification and Experimental Production of Arteriosclerosis. Brit. Med. Jour., 1906, p. 1767.

The earlier experiments, in which injuries, mechanical and chemical, were applied to the vessels, do not concern us here, nor shall I consider the experiments of Lewaschew, Fränkel, and Barvoets, who produced extensive lesions in vessels by resection of nerves (sciatic nerve). Von Czyhlarz and Helbing[39] have conclusively shown that the lesions produced by these observers are of a purely inflammatory character and will not ensue if all inflammation is prevented.

Returning to the aortic lesions of the adrenalin type, there has been much discussion as to the mechanism by which these lesions are produced, more especially whether increased blood pressure—hypertension—or toxic influences are to be held responsible. If we accept the view that the lesions in question are really produced by the substances introduced into the circulation, then the theory that hypertension is the sole or even the main factor in the process seems untenable. The mere fact that similar results have been obtained by substances tending to lower blood pressure, as well as by others that have no influence whatever upon pressure, is sufficient to upset the hypertension theory. It is, besides, hardly conceivable that a sudden, even a very considerable, rise of pressure, if of short duration, could cause such extensive changes. Josué,[40] it is true, claims that repeated injections of adrenalin keep up the pressure above normal for a long time. This is denied by others. That toxic influences are at work is proved not only by the known toxic character of many of the chemicals employed, but also by the cachexia which frequently appears, and the marked toxic and irritant lesions found in other organs besides the aorta, such as the liver, the heart, the kidneys, etc., which it is not within the scope of this paper to describe. Even adrenalin, besides its pressure-raising quality, has a distinctly toxic influence on various organs and also on the blood itself, according to Loeper and Grouzon.[41]

In view, however, of the startling figures brought forward by Miles, and after deliberate and careful study of all the results, both positive and negative, at present available, it may well be questioned if the aortic lesions observed are the result of experiment, or if they are not rather simply the natural outcome of spontaneous disease without any causal relation to experimental procedures. Klotz has shown that long before macroscopic lesions become visible minute degenerations of the muscle cells and elastic fibers, even the beginnings of calcification, may exist. It may well be conceived that the toxic elements experimentally introduced into the circulation, if they have any effect at all, act simply as a more or less powerful stimulus upon an already diseased aorta and render active and manifest the pathological condition until then merely latent. A series of experiments by Dr. Hensel and myself, not yet published, on about 100 rabbits, with various toxic substances, taking into account the numerous negative as compared to the positive results, has suggested this conclusion to us even before the publication of Dr. Miles' paper. Fischer seems to entertain similar opinions. In the present state of our knowledge it is perhaps the most plausible solution of the difficulty, but before the question can be finally decided much more investigation will be necessary.

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[39] Experimentelle Untersuchungen über die Beziehung von Nervenlesionen zu Gefässveränderungen. Centralbl. f. Path. u. path. Anat., 1897, viii. 849.

[40] La pression artérielle chez le lapin a la suite d'injections repetées d'adrenaline dans les veines. Soc. de Biol., 1905, 319.

[41] L'action de l'adrenaline sur le sang. Arch. de med. exp, anat. et path. 1904, p. 83.

Do these pathological processes as found in the rabbit's aorta bear any relation to human arteriosclerosis? The majority of German authors hold the opinion that they have nothing whatever to do with human arteriosclerosis; others, especially those of the French school, unhesitatingly consider them as identical with human atheroma. Though, of course, it is far beyond the limits of this paper to enter into any details concerning the various theories of arteriosclerosis, or to discuss, no matter how briefly, the innumerable problems—physiological, pathological, histological, and clinical—offered by the vascular system,[42] it will nevertheless be necessary to state in as few words as possible what we conceive to be the present status of our knowledge of human arteriosclerosis, or "atherosclerosis," as it is aptly named by Marchand.[43] There has been a marked tendency, especially since the work of Jores[44] and his followers, to consider, when speaking of arteriosclerosis, mainly the characteristic lesions in the aorta, and to relegate to an entirely different class the calcifications and other changes in the media in other arteries, especially in the peripheral vessels, as described by Mönckeberg. This view is perhaps, as Klotz remarks, too narrow in its limitations. The clinical manifestations of arteriosclerosis are not as yet as sharply defined in all their details as may be desirable, but there is a vivid and distinct conception of human arteriosclerosis in the mind of every physician, and though perhaps somewhat loosely handled at times, is nevertheless a clinical entity dealing with the vascular system as a whole, and not merely with the aorta.

It may then be said very concisely, with Aschoff,[45] that the essential and cardinal point in the pathology of atheroscleorsis is impairment and subsequent degeneration of the elastic elements. Atherosclerosis is mainly a hyperplastic and degenerative, and in no wise an inflammatory process. Endarteritis proliferans annd obliterans, though often, no doubt, associated with true atherosclerosis, must be classed separately. The same holds good for certain specific infections, especially syphilis. The latter may perhaps be a factor in bringing about general arteriosclerosis, but the easily recognized and characteristic luetic lesions as they appear in the aorta and the cerebral vessels must be separated from typical arteriosclerosis.

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[42] A full discussion of the pathology of arteriosclerosis and its more recent literature is given by Thorel, Lubarsch, and Ostertag, Ergebnisse, 1903, 1; 1907, ii.

[43] Ueber Arteriosklerose. Kongress f. innere Medizin, xxi.

[44] Wessen und Entwickelung der Arteriosklerose, 1903.

[45] Ueber Atherosklerose und andere Sklerosen des Gefäss-systems. Beihefte z. med. Klinik, 1908, iv, Nr. I.

It is being more and more clearly recognized that different vessels have different functions, and, therefore, also different structure, and perform their work under different physical and mechanical, and possibly different chemical conditions. The aorta, for instance, especially the ascending portion, receives every moment a large volume of blood direct from the heart under high pressure and with undoubtedly numerous cross-currents and vortices, for which it must provide an even distribution. The femoral, on the other hand, at great distance from the heart, must pass the blood to the smaller arteries with sufficient force and impetus to secure uniform tension down to the capillaries. Aschoff[46] divides all arteries into two groups according to their differences in structure: those of the elastic type, aorta, carotids, and iliacs, and those of the muscular type, the majority of the peripheral arteries. In vessels of the elastic type, whose most important function it is to withstand pressure and prevent overdistention, the intima with its elastic and connective tissue elements is the more important factor; while in vessels of the second group, that have special propelling functions, the muscular elements of the media are more highly developed. It is conceivable that physical strain, toxic influences, and the like may cause different reactions in different vessels according to their type of structure and of function.

Ever since Thoma's investigations the growth and development of the bloodvessels has been the object of considerable careful research. It is generally accepted now that there is a continuous increase in length as well as a regular and progressive development of the structural elements of the aorta and larger vessels, especially of the connective and elastic tissue of the intima. With the increased demands on the vessel, reinforcements of the elastic and fibrous and also of the muscular elements keep equal step, so that under the influence of normal conditions of pressure and longitudinal and lateral tension, what may be called a physiological hyperplasia of the intima takes place. This physiological process of growth reaches its climax usually in the third decade of life. The very valuable and exact measurements of Scheel[47] corroborate the results obtained by others (Bennecke and Suter). According to these investigators the completion of normal growth is followed almost immediately by the first signs of regression. Thayer and Fabyan[48] have come to similar conclusions from histological studies of the radial artery. Slowly but surely the elasticity of the arteries begins to decrease, the vessels to dilate somewhat; in other words, the first faint senile changes appear very soon after maturity is reached, and lead, in some individuals sooner, in others later, inevitably to arteriosclerosis.

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[46] Generally speaking, arteries may be conceived as consisting of two concentric tubes: an inner fibro-elastic tube and an outer muscular tube.

There is almost a consensus of opinion that pressure and tension are the main factors in the development both of the physiological and the pathological alterations in the arteries, and that, as Albrecht[49] puts it, mechanical impairment is the underlying and primary cause of arteriosclerosis. That hard physical labor and strain tend to accelerate the normal "physiological" advent of arteriosclerosis seems more than likely. Thayer and Brush,[50] in an analysis of the records of nearly 4000 cases, find that heavy physical labor gives a very high percentage of palpable radial arteries. Baumler[51] records the interesting observation that left-handed persons often develop arteriosclerosis of the left radial, the right being normal. But arteriosclerosis is not merely the result of overstrain, of wear and tear of the arteries; is not merely an "Abnutzungs-Krankheit," as the Germans call it. There must be, beyond doubt, other and probably numerous factors tending to impair the elasticity and lower the power of resistance of the vascular walls. We cannot close our eyes to the fact that we find every now and then some fortunate ones who live to a high old age, often under great stress and strain, without showing until almost the very end of life any very marked symptoms of arteriosclerosis. On the other hand, arteriosclerosis is found with increasing frequency, as more attention is paid to the subject, in youthful individuals. Without attaching too much importance to the well-known case of Bryant and White,[52] in which all the arteries of the body with the exception of those of the head were sclerotic and calcified, or the case of Durante,[53] in which atheroma of the pulmonary artery was found, evidently prenatal, in a seven months child that died of umbilical infection shortly after birth, there are the figures of

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[47] Gefässmessungen und Arteriosklerose. Virchow's Arch., 1908, cxci, Heft i, Nr. 1.

[48] Studies in Arteriosclerosis, with Special Reference to the Radial Artery. Trans. Assoc. Amer. Physicians, 1907, xxii, 694.

[49] Uber Arteriosklerose. Münch. med. Woch., 1906, 332.

[50] The Relation of Acute Infections to Arteriosclerosis. Jour. Amer. Med. Assoc., 1904, p. 726.

[51] Ist die Arteriosklerose eine Allgemein Krankheit. Berl. klin. Woch., 1905, Nr. 44a.

[52] A Case of Calcification of the Arteries, etc., in a Child aged Six Months. Guy's Hospital Reports, lv, 18.

[53] Bulletin de la Soc. Anat. 1899, p. 97.

v. Simnitzky,[54] who has confined his attention only to the aorta, but finds the early stages of arteriosclerosis in individuals under twenty-five years of age in at least 27.5 per cent. of all cases examined.

Huchard[55] and his school make the acute infectious diseases of infancy and childhood largely responsible for the arteriosclerosis of later years. Hofbauer[56] saw arteriosclerosis following measles in a boy aged seventeen years. The studies of Thayer[57] and of Thayer and Brush[58] tend to show that, besides hard work, typhoid fever and alcoholism have a marked effect upon the early development of arteriosclerotic symptoms. Richard Wiesner[59] frequently found extensive calcification in the coronaries of youthful individuals between the ages of fifteen and twenty-three years after endocarditis or prolonged osteomyelitis. Wiesel[60] made extensive studies of the heart and bloodvessels of youthful persons in many of the infectious diseases—typhoid fever, scarlet fever, measles, diphtheria, sepsis, pneumonia, osteomyelitis, etc. He found lesions in the arteries mainly in the media and in many respects resembling experimental lesions in rabbits. According to Lortat and Sabareanu[61] diseases of the thyroid gland and thyroidectomy have a decided effect upon the early and extensive development of arteriosclerosis. That alcoholism, lead, tobacco, and other intoxications tend toward the development of arterial lesions is highly probable, though not as yet positively proved. Gout and diabetes may also be mentioned as causing a marked disposition toward arteriosclerosis. According to Romberg,[62] purely psychic and emotional factors, by causing frequent, rapid, and very violent oscillations of pressure, tend in the same direction. Rumpf,[63] M. Fränkel,[64] Burwinkel[65] and Gazert[66] collect evidence to show that metabolic and chemical disturbances, both local and systemic, are often concerned in the process. Chronic nephritis has long been recognized as a cause of arteriosclerosis. Lastly, clinical observation points to hereditary disposition as an important etiological element.

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[54] Ueber die Häufigkeit von Arterioskleroticshen Veränderungen in der Aorta jugendlicher Individuen. Ztschr. f. Heilkund., 1903, xxiv, 177.

[55] Les causes de l'arterio-sclerose et des cardiopathies arterielles. Rev. gén. de clinique et de thérapeutique, 1891.

[56] Wien. klin. Woch., 1903, Nr. 34.

[57] The Effects of Typhoid Fever on the Heart and Vessels. AMER. JOUR. MED. SCIENCES, March, 1904.

[58] Relations of Acute Infections to Arteriosclerosis. Jour. Amer. Med. Assoc., 1904, p. 26.

[59] Ueber Veränderungen der Koronargefässe bei Infektionskrankheiten. Wien. klin. Woch., 1906, p. 725.

[60] Ueber Gefässveranderungen im Verlaufe akuter Infektionskrankheiten. Wein. med. Woch., 1906, p. 15; Ueber Veränderungen am Zirkulationsapparate, speziell des peripheren Gefäss-systemes bei Typhus abdominalis. Ztschr. f. Heilk., 1905, p. 107.

[61] Pathogénie de l'athérome artériel et thyroidectomie. Soc. de Biol. lvii, 444.

[62] Ueber Arteriosklerose. Kongress f. innere Medizin, 1904.

[63] Ueber Arteriosklerose. Münch. med. Woch., 1905, p. 46.

[64] Ueber Theorie und Behandlung der Arteriosklerose. Wien. klin. Rundschau, 1905, p 30.

[65] Aetiologie und allgemeine Therapie der Arteriosklerose. Berl. klin. Woch., 1905, p. 16.

[66] Ueber den Fett- und Kalkgehalt der Arterienwand bei Atheromatose und Arteriosklerose. Deut. Arch. f. klin. Med., 1899, lxii, 390.

SUMMARY. Arteriosclerosis, or, to use the better term, "atherosclerosis," may be designated as a morbid condition of the bloodvessels closely following and allied to the physiological process of development, growth, and senescence of the vascular system, and governed by the same laws. It may without exaggeration be said that atherosclerosis, viewed as a disease, is merely the anticipation in time, extent, and intensity of the normal "physiological" condition of senility. In physiological terms it may be expressed as an impairment or loss of elasticity and of functional adaptability of the vessel walls. Pathologically it is a process of degeneration of the elastic and muscular elements of the vessel walls, associated with compensatory and reparative hyperplasias and hypertrophies principally of the connective tissue elements, and often tending to calcifications and ulcerative processes. The etiological factors that determine its earlier or later onset, its localization, whether more general or more restricted to certain limited portions of the vascular system, and very probably also, at least in part, its histological structure, are manifold. Heredity and physical overstrain ("Abnutzung") in its numerous variations must certainly play an important part. It is most probable that bacterial and other infections, and intoxications with organic as well as inorganic poisons are important etiological factors, and may possibly have considerable influence on the localization as well as on the histological type of the arteriosclerotic process. We are disposed to conceive atherosclerosis, therefore, as a clinical entity. The various types of vascular degeneration briefly mentioned above—the typical lesions in the aorta, the degeneration and calicification in the media of the pulmonary artery, and especially of the peripheral vessels—with all their sequels, are all gathered together into this one large group. They all have a common etiology and are closely allied in their physiological and pathological relations. From this point of view the recent experimental researches with adrenalin, nicotine, and all the other substances would seem to have a direct bearing upon the problem of arteriosclerosis, inasmuch as they appear to demonstrate the effect of toxins of various kinds upon the development of atherosclerotic lesions in the rabbit. They would also appear to go far toward establishing a most important fact, namely, that different kinds of toxic agents can produce lesions of different histological character (bacterial toxins on the one hand and the adrenalin group of poisons on the other). It must be confessed, however, that the element of uncertainty as to how much is due to experiment and how much is spontaneous and independent of all experimentation, which clings to all of these investigations, very seriously impairs the value of all of this work and compels for the present, and until further investigation has cleared up these questions, a suspension of judgment, or at least a very guarded and provisional acceptance of these results. It may confidently be expected, however, that further research along similar lines, with a study of spontaneous atherosclerosis, especially in carnivorous animals, both wild and domesticated, and its comparison with the human, together with the experimental investigation of the effect of bacterial infection and of toxins on other animals besides rabbits, will materially assist in advancing our knowledge and throwing some light into much that is still very obscure.

THE BACTERIOLOGY OF THE PUERPERAL UTERUS.

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The germ content of the uterus has been controversial ground for years. The question has been investigated by many since the time of Doederlein with the most varied results, to be explained, in our opinion, upon the ground of errors in technique. Probably the earliest investigator in this field was Myerhofer, who, in 1865, employed suction by means of a glass tube. He was always able to demonstrate cocci and bacilli if the case were febrile, but he did not find them in afebrile cases. Doederlein, in 1887, reported a series of 30 cases with normal temperature. In 27 of these the lochia was sterile, while in 3 bacilli were present, streptococci being identified once. He drew the conclusions from his study: (1) That in normal cases the uterine lochia is sterile; (2) that microörganisms are almost always present in severe cases of puerperal infection; (3) that infection is not always due to lack of care on the part of the physician. Von Ott and Czerniewski, in 1888, arrived at the same conclusions, but the latter held that the streptococcus might be present in the lochia of normal cases in rare instances without symptoms.

In contradistinction to the above, we wish to call attention to the statistics contributed by Stolz, who found streptococci in the vaginal secretion of three normal pregnant women, while in a series of women with abnormal vaginal secretion during pregnancy streptococci were present in several instances. In studying the puerperal uterus, he found that on the ninth day, in a series of 156